UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

[Revised for error on page 16 - supercedes TXR# 0055233]

MEMORANDUM

Date: ~~August 12, 2009~~ September 02, 2009

SUBJECT: **Third Peer Review of Hexythiazox (Savey):** Report of the Cancer Assessment Review Committee

PC Code: 128849
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
TXR No.: ~~0055233~~ 0055255
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.:
40 CFR: N/A

FROM: Jess Rowland, Co-chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Mary Manibusan Co-chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Mike Metzger, Chief
Donna Davis, Risk Assessor
Registration Action Branch VII
Health Effects Division (7509P)

Barbara Madden
RIMUERB, Registration Division (7505P)

Olga Odiott, RM 13
Insecticide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on June 10, 2009 to re-evaluate the cancer classification of Hexythiazox (Savey) in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the Final Cancer Assessment Document.

Recvd in RMC 9/8/2009

CANCER ASSESSMENT DOCUMENT

THIRD EVALUATION OF THE CARCINOGENIC POTENTIAL OF

HEXYTHIAZOX
(SAVEY)

PC Code 128849

August 12, 2009

Final

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

HEXYTHIAZOX (SAVEY) CANCER ASSESSMENT DOCUMENT FINAL

DATA PRESENTATION: Jess Rowland, CARC Co-chair

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Lori Brunsman, Statistician

Marion Copley

Kit Farwell

Ray Kent

Mary Manibusan , Co-Chair

Karlyn Middleton

Rob Mitkus

Esther Rinde

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Kimberly Nesci (RD), Michael Khan (HED/TEB), Anwar Dunbar (HED/RABI), Mike Metzger (HED/RAB VII)

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EXECUTIVE SUMMARY

On June 10, 2009, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) met to re-evaluate the carcinogenic potential of hexythiazox (Savey) in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). This was the third cancer review of this chemical. The reclassification, using the updated cancer guidelines, was requested due to an IR-4 petition for a new use on potatoes grown in Washington, Oregon and Idaho and a registrant petition for amended uses for field corn and tree nuts.

Background: On October 15, 1986, the HED's Toxicology Branch Peer Review Committee met to evaluate the carcinogenic potential of hexythiazox. A consensus for classification was not reached. The proposed B2/C classification with a linear low-dose for quantification was recommended (Memo, E. Rinde dated February 2, 1987, TXR No. 0054487).

On December 15, 1987, the Agency's FIFRA Scientific Advisory Panel (SAP) reviewed the B2/C classification of hexythiazox and concluded that the weight of evidence for carcinogenicity of hexythiazox is most consistent with Category C. This classification was based on the lack of induction of malignant tumors in rats, the low incidence of benign mammary tumors in control rats, and the lack of mutagenicity (SAP Report, dated 12/23/1987).

On January 13, 1988, HED's Cancer Peer Review Committee (CPRC) met to examine the issues raised by the SAP with respect to the classification of hexythiazox. Based on the increased incidence of malignant, and combined benign/malignant liver tumors in the B6C3F1 mouse, the CPRC classified hexythiazox as a Category C chemical (possible human carcinogen), with a quantitative risk assessment (Memo, E. Rinde, 3/16/88, TXR No. 0054489).

Carcinogenicity

Mouse

- Administration of hexythiazox resulted in the induction of liver tumors in female B6C3F1 mice. There were significant increasing trends for liver adenomas ($p<0.01$), carcinomas ($p<0.05$) and combined adenomas/carcinomas ($p<0.01$). There were also significant differences in the pair-wise comparison of the high dose with the control for adenomas ($p<0.01$), carcinomas ($p<0.05$), and combined adenomas and carcinomas ($p<0.01$). There was no evidence of carcinogenicity in male mice at any dose level. **The CARC considered the liver tumors, seen at the high dose, in female mice to be treatment-related.**

- *Adequacy of Dosing*: Dosing at the high dose in the mouse study was considered to be adequate in both sexes for assessing the carcinogenic potential of hexythiazox. This was based on decreased body weight gains, increased absolute/relative liver weights in males and/or females, and the presence of non-neoplasic liver nodules.

Rat

- Administration of hexythiazox resulted in the induction of tumors of the mammary gland in male Fischer 344 rats. There was a significant increasing trend at $p<0.01$ and a significant difference in the pair-wise comparison of the high dose with the control for fibroadenomas at $p<0.05$. There was no evidence of carcinogenicity in female rats at any dose level. **The CARC considered the mammary gland tumors in male rats to be treatment-related.**

- *Adequacy of Dosing:* Dosing at the high dose was considered to adequate in both sexes for assessing the carcinogenic potential of hexythiazox based on the decreases in body weight and increases in testicular and ovarian weights.

Mutagenicity

There is no mutagenic concern for hexythiazox.

Structure Activity Relationship

No closely related structural analogs were identified.

Mode of Action

No mode of action data were submitted for this chemical.

Classification and Quantification of Carcinogenic Potential

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified hexythiazox as **"Likely to be Carcinogenic to Humans"**. This classification was based on tumors in 2 species: a treatment-related increase in benign and malignant liver tumors in female mice and the presence of mammary gland tumors (fibroadenomas) in male rats, with incidences exceeding that of the laboratory's historical controls. Although the rat mammary gland tumors were benign, they are uncommon in male rats (the laboratory's incidence rate was only 0-2%). There is no mutagenic concern for hexythiazox.

The CARC concluded that the evidence as a whole was not strong enough to warrant the use of a linear low dose extrapolation model applied to the animal data (Q_1*) for a quantitative estimation of human risk, based on the common liver tumors (benign and malignant) only observed in high dose female mice, and benign mammary gland tumors, only observed in high dose male rats. Also, there is no mutagenic concern for hexythiazox.

The NOAEL of 2.5 mg/kg/day, from the one year toxicity feeding study in the dog, used for establishing the chronic Reference Dose (RfD) is approximately 65-fold lower than the lowest dose (163 mg/kg/day) that induced tumors. Thus, the chronic RfD of 0.025 mg/kg/day would be

protective of all chronic effects including potential carcinogenicity of hexythiazox.

I. INTRODUCTION

On June 10, 2009, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) met to re-evaluate the carcinogenic potential of hexythiazox (Savey). This was the third cancer review of this chemical. The reclassification using the updated cancer guidelines was requested due to an IR-4 petition for a new use on potatoes and a registrant petition for amended uses for field corn and tree nuts.

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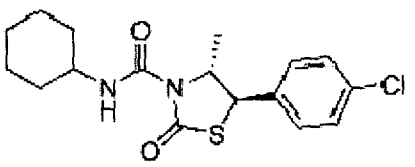
II. BACKGROUND INFORMATION

Chemical common name:	Hexythiazox
Type of pesticide:	Acaracide
PC Code:	128849
CAS Number:	78587-05-0
Chemical name:	Trans-5-(4-chlorophyl)-N-cyclohexyl-4methyl-2-oxothiazolidine-3-carboxamide.

Structure:



III. EVALUATION OF CARCINOGENICITY STUDIES

1. Chronic Toxicity/Carcinogenicity Study in the Mouse

Reference: Two-year Dietary Chronic Toxicity/Oncogenicity Study in B6C3F1 mice. Testing Facility: Biosafety Research Center (AN-PYO Center) Shizuokaken, Japan. (MRID Nos. 00147577, 00156896).

A. Experimental Design

In a combined chronic toxicity/carcinogenicity study in mice, groups of B6C3FI mice (80/sex/dose) (interim sacrifice of 10/mice/sex/group at 26, 52, and 78 weeks) received NA-73 technical (98.2% a.i.; Batch No. SAF-25) in the diet at 0, 40, 250, or 1500 ppm (0, 6.72, 41.6, or 267 mg/kg/day for males; 0. 8.38, 51.2. or 318 mg/kg/day for females) for 104 weeks. Forty additional mice (20/sex) in the control group were sacrificed at zero time to obtain baseline hematology and biochemical parameters.

B. Discussion of Survival and Tumor Data

Survival

The number of treated animals surviving to the end of the study was comparable to that of the respective controls (males: 78%, 76%, 74%, 76%; females: 84%, 88%, 90%, 88%, for controls to high dose). No effects were seen in the 40 or 250 ppm dose groups.

Tumors

Table 1. Liver Tumor Rates [+] and Exact Trend Test and Fisher's Exact Test Results (p-values)

Tumor Type	Dose (ppm)			
	0	**40**	**250**	**1500**
		Males		
Adenomas (%)	17/60 (28)	16/60 (27)	18/60 (30)	22/60 (37)
Carcinomas[#] (%)	14/60 (23)	13/60 (22)	13/60 (22)	18/60 (30)
Combined (%)	31/60* (52)	29/60 (48)	31/60 (52)	40/60 (67)
		Females		
Adenomas (%)	8/60** (13)	2/60 (3)	7/60 (12)	20/60** (33)
Carcinomas[#] (%)	0/60* (0)	3/60 (5)	3/60 (5)	5/60* (8)
Combined (%)	8/60** (13)	5/60 (8)	10/60 (17)	25/60** (42)

[+] Number of tumor bearing animals/Number of animals examined (excluding those that were sacrificed at week 26, and also excluding those that were sacrificed at week 52, before the appearance of the first tumor.)

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If * , then $p < 0.05$. If ** , then $p < 0.01$.

There was no evidence of carcinogenicity in male mice at any dose level. Female mice had significant increasing trends for adenomas ($p<0.01$), carcinomas ($p<0.05$) and combined adenomas/ carcinomas ($p<0.01$). In addition, there were significant differences in the pair-wise comparison of the high dose with the control for adenomas ($p<0.01$), carcinomas ($p<0.05$), and combined adenomas/carcinomas ($p<0.01$). (Memo, B. Fisher, Savey, 1/15/88, TXR No. 0055240).

When compared to historical controls of the testing facility, the incidences of liver tumors at the high dose in the current study exceeded those of the historical controls for these tumors in the study facility. (See following table.)

1) Incidence of Liver Neoplasms in B6C3F1 Mice abstracted from investigators'[1] historical control data

		78 + 104 weeks %	104 weeks %	Range %
Adenomas	M	22.7	25.7	18-34
	F	8.2	8.9	4-14
Carcinomas	M	9.4	10.7	6.7-16
	F	1.7	2.1	0-8

[1]Biosafety Research - These data were taken from Appendix D of Reviewer's package.

C. Non-neoplastic lesions and other findings

The incidence of preneoplastic hepatic nodules was also significantly increased in both sexes at 1500 ppm.

D. Adequacy of the Dosing for Assessment of Carcinogenicity (taken from TXR No. 0054487)

The CARC concurred with the previous decision that the dose of 1500 ppm was adequate to assess the carcinogenic potential of hexythiazox. This was based on decreases in body weight (11.5%)/body weight gain(18%) in males, increased liver weights (both sexes), and non-neoplastic lesions (liver nodules) (both sexes) at the high dose. Mean body weight and body weight gain in high dose females were comparable to controls

2. Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Lifetime Dietary Toxicity and Oncogenicity Study in Fischer 344 Rats. Testing Facility: International Research and Development Corporation., Mattawan Michigan. (MRID No. 00146559),

A. Experimental Design

In a combined chronic toxicity/oncogenicity study in rats, groups of Fischer 344 rats (80/sex/dose) received NA-73 (Lot No. SAF-25, 93.9% a.i.) in the diet at 0, 60, 430, or 3,000 ppm (0, 3, 23, or 163 mg/kg/day for males; 0, 4, 29, or 207 mg/kg/day for females) for two years. Thirty rats/sex/dose were used for clinical pathology and drinking water analysis and 10 rats/sex/dose were used for interim 12-month sacrifice.

B. Discussion of Survival and Tumor Data (taken from TXR No. 0054487)

Survival

There were no major differences in survival among the groups (males: 50/70, 57/70, 59/70, 53/70; females: 57/70, 49/70, 61/70, 56/70, controls to high dose).

Tumors

Table 2. Mammary Gland Tumor (fibroadenomas) Rates [+] and Cochran-Armatage Trend and Fisher's Exact Test Results (p- values)

	Dose (ppm)			
	0	**60**	**430**	**3000**
Males				
Fibroadenomas (%)	0/70 (0)**	1/69 (1)	2/69 (3)	6/67 (9)*
Fibromas (%)	0/70 (0)	0/69 (0)	0/69 (0)	1/67 (1.5%)
Females				
Fibroadenomas (%)	6/70 (9)	3/68 (4)	1/70 (1)	5/70 (7)
Fibromas (%)	0/70 (0)	0/68 (0)	0/70 (0)	0/70 (0)

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If * , then $p < 0.05$. If ** , then $p < 0.01$.

In male rats, there was a significant increasing trend ($p<0.01$) and a statistically significant difference in the pair-wise comparison of the high dose group with the controls ($p<0.05$). No increase in fibroadenomas was seen in female rats. Also, there was no increase in mammary

gland fibromas in male or female rats.

The historical control data are presented below. The incidence at the high dose exceeded both the concurrent control (0%) and the IRDC laboratory control (0-2%).

2) Incidence of Benign Mammary Gland Tumors in Fischer 344 Rats

		IRDC[2]	Solleveld, et al.[3]	NTP Survey of Interlab. Variability[4]
		Range %	%	Range %
Adenomas	M	0-2	-	-
	F	1.7-6	-	-
Fibroadenomas	M	0-2	2.2, 13.4	0-4 , 0-8
	F	7.5-22	24.1, 57.3	see App. H

[2]These data were taken from Appendix F
[3] " " " " " " G
[4] " " " " " " H

C. Non-neoplastic lesions and other findings (taken from TXR No. 0054487)

No treatment-related non neoplastic lesions were seen in either sex at any dose level.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC concluded that the doses tested in male and female rats were adequate to assess the carcinogenic potential based on decreases in body weight and increases in testes and ovarian weights at the high dose.

Body weight was significantly decreased (3-8%/3-13%, males/females) in both sexes throughout the study in the high dose group. Body weight gain was also decreased (1 1%/17%, males/females) in both sexes at 3000 ppm.

IV. Toxicology

Metabolism (taken from TXR No. 0054487)

Hexythiazox was rapidly absorbed from the GI tract after oral administration in the rat. Almost all the radioactivity was recovered by 72 hours post administration of ^{14}C- Hexythiazox; 30% in the urine of both sexes, and 66.5% and 59.8% in the feces of male and female rats, respectively. Four to 10% of ^{14}C remained in the tissues; among tissues examined, the residue of hexythiazox was highest in the fat, with females containing twice as much as males. Pharmacokinetic analysis

indicates plasma concentration decay follows first order kinetics.

The undegraded parent compound was the major component (consisting of 20% of the dosed radioactivity); the major metabolite was PT-1-8 (cis) (10-12% of the dosed radioactivity).

2. Mutagenicity

Five genetic toxicology studies were available. All *in vitro* studies were acceptable. Results indicate that hexythiazox was not mutagenic in bacteria or Chinese hamster ovary (CHO) cells; was negative for chromosome aberrations in CHO, did not cause unscheduled DNA synthesis (UDS) in primary rat hepatocytes, and did not increase the frequency of micronucleated polychromatic erythrocytes in a mouse micronucleus assay. Executive Summaries from the acceptable studies are presented below:

GENE MUTATION

In a reverse gene mutation in bacteria (MRID No. 44955710), duplicate cultures of five histidine auxtrophic strains (his$^-$) of *Salmonella typhimurium* (TA98, TA100, TA 1535, TA1537, and TA1538) and the tryptophan auxtrophic strain (*try*$^-$) of *Escherichia coli*. WP2 *u*vra were exposed in a plate incorporation assay to the technical formulation of SAVEY miticide dissolved in dimethylsulfoxide (DMSO) at seven concentrations (100 to 6400 *u*g/plate), in the presence and absence of metabolic activation provided by rat liver microsomes induced by phenobarbital and 5,6-benzoflavone. In addition to treated cultures containing only the vehicle (DMSO), other cultures were exposed to strain-specific mutagens to serve as positive controls for the nonactivation and activation treated cultures. After 48 hours incubation at 37°C, all treated cultures were terminated, revertants (to *his*$^+$ and *try*$^+$) counted and compared to vehicle counts. NA-73 (hexythiazox) was tested up to the limit of solubility (3200 to 6400 *u*g/plate), but showed no significant inhibition of cell growth. **Revertant colonies at all doses from 100 to 6400 *u*g/plate were not increased over the vehicle controls.** Therefore, the test article is not mutagenic in the conventional battery of *Salmonella* strains nor in *E. coli* WP2 *u*vrA with/without activation by phenobarbital + benzoflavone.

In two independent mammalian gene mutation assays (MRID No. 00155154), duplicate cultures of Chinese hamster ovary (CHO) cells were exposed to 5 concentrations (2, 10, 20, 50, 200 *u*g/mL) of SAVEY technical (98.9% a.i.) in dimethylsulfoxide (DMSO) for 18 hours without activation, and for 5 hours (plus an additional 19 hours in treatment-free medium) at five concentrations (5, 20, 50, 200, 400 *u*g/mL) in the presence of metabolic activation provided by Aroclor 1254 induced rat liver homogenate (S9-mix). Following this initial treated incubation, the cells were incubated an additional 7 days in treatment-free medium, (the expression period for HGPRT mutants), then for 7 days in a medium containing the purine analog, 6-thioguanine (6-TG), which converts to the toxic monophosphate metabolite, lethal to nonmutant cells. Presumptive mutants having lost HGPRT (hypoxanthine guanine phosphoribosyl transferase) activity are resistant to this metabolite, and are counted as mutant colonies. In addition to cultures exposed to vehicle alone (DMSO), additional cultures were treated with

ethylmethanesulfonate (EMS, 200 *u*g/mL) and dimethylnitrosamine (DMN, 100 *u*g/mL) to serve as positive controls for the nonactivated and activated test series. SAVEY technical was tested up to precipitating (60 *u*g/mL and above) and severely toxic levels (200 *u*g/mL/-S9; 400 *u*g/mL/+S9) in both initial and confirmatory assays. **However, no increase in mean mutant frequency in SAVEY-treated cultures over vehicle controls was recorded at any concentration.** Positive controls responded appropriately with significantly increased mutant frequencies. Hence, SAVEY technical is considered negative for forward mutation at the HGPRT locus in CHO cells.

CHROMOSOME ABERRATIONS

In repeat chromosome assays (MRID No. 00156894), duplicate cultures of Chinese hamster ovary (CHO-WBL) cells were exposed to NA-73 technical (purity not specified in the absence of mammalian metabolic activation for 7.6, 17.5 or 27.6 hours, followed by 2.5 hours in medium containing 0.1 *u*g/mL of the mitotic inhibiting alkaloid, Colcemid, to collect dividing cells in metaphase. Cultures under conditions of metabolic activation provided by Aroclor 1254-induced rat liver microsomes, S9-mix (S9 plus generating cofactors) were exposed to test article for only 2 hours, followed by further incubation in treatment- and S9-free medium for 7.8, 17.8 or 27.8 hours with 0.1 *u*g/mL Colcemid present during the last 2.5 hours of incubation. Metaphase cells were then harvested and prepared for cytogenetic analysis. In addition to negative (medium only) and vehicle controls, additional cultures for each phase of the assay were treated with the mutagens, mitomycin-C (MMC, 500 ng/mL and 1.0 *u*g/mL), and cyclophosphamide (CP, 25 *u*g/mL and 50 *u*g/mL), to serve as positive controls for the nonactivation and activation test series, respectively. NA-73 was tested up to levels of precipitation (167 and 500 *u*g/mL +/-S9) accompanied by severe toxicity in nonactivated cultures, and moderate toxicity (60% decrease in monolayer confluency at 50 µg/mL -S9) at analyzable concentrations (5 to 16.7 *u*g/mL S9; 16.7 to 50 *u*g/mL+S9). **However at no concentration or time period were frequencies of chromosome aberrations significantly increased over medium or vehicle controls.** The positive controls responded appropriately in each phase of the study. Therefore, the test article is considered negative for inducing chromosomal aberrations under conditions of this assay.

OTHER MUTAGENIC MECHANISMS

In an unscheduled DNA synthesis (UDS) assay (MRID No. 00156893), primary hepatocyte cell cultures were established *in vitro* on coverslips from a male rat (using the Williams procedures of 1977 and 1980), and exposed for 18-19 hours to seven concentrations of NA-73 (98.4%) ranging from 2.5 to 250 *u*g/mL in medium containing tritiated-thymidine. At harvest, replicate coverslips were developed for nuclear grain development on stained preparations. In addition to the vehicle, dimethylsulfoxide (DMSO) controls, other cultures were treated with 2-acetylaminofluorene (AAF, 0.1 *u*g/mL) to serve as positive control. UDS was scored by counting nuclear silver grains and subtracting the mean number of grains in adjacent cytoplasmic areas as background. Two trials were initiated with 3 replicates per group allocated for determination of UDS, and 2 for cell viability. The first trial had to be terminated prior to completion because of stated ". . . poor quality of cell preparations." The second trial (with cells

from a second male rat) produced dose-related cytotoxicity at the higher dose levels of 50, 100 and 250 ug/mL (the last lethal to all cells), but no increases in mean UDS in NA-73-treated cultures over background or concurrent vehicle controls at any level. These data were presented as a summary table of mean values (on p. 23 of the initial study report). The investigators concluded that the test article does not induce UDS in primary rat hepatocyte cultures. However, the Agency classified the study as reported as unacceptable, because additional information was required to permit appropriate analysis of the data. Additional data were submitted by the registrant as provided by the performing laboratory (Amended Report, August, 1984, Second Amended Report, May 1985). **Thus, the Agency has concluded that there was no evidence (or a dose-related positive response) that unscheduled DNA synthesis, as determined was induced in primary hepatocyte culture of the rat.**

In mouse bone marrow micronucleus assay (MRID 45480101), five ICR mice/sex/dose/harvest time were treated via intraperitoneal injection (i.p.) with hexythiazox technical (99.0% a.i., Lot # IB-3179) in corn oil at concentrations of 0, 500, 1000 or 2000 mg/kg body weight with sacrifice at 24 hours at all three doses and additionally at 48 hours at 2000 mg/kg. Bone marrow cells were harvested immediately following sacrifice.

Hexythiazox technical was tested to the limit dose of 2000 mg/kg body weight. No mortality was seen in the study but virtually all mice in the two higher dose groups showed lethargy and piloerection following treatment. At the 24 hour sacrifice time, the PCE to total erythrocyte ratio at 2000 mg/kg was reduced by 17% and 24% compared to the solvent controls in males and females, respectively, indicating that the test material reached the bone marrow. The ratio in males but not females was also reduced a similar amount at the two lower doses. The mean numbers of micronucleated PCEs per 1000 PCEs of the solvent controls at the 24 hour sacrifice time were 0.4 ± 0.42 and 0.4 ± 0.22 in males and females, respectively, and at the 48 hour sacrifice time, were 0.3 ± 0.45 and 0.3 ± 0.27 in males and females, respectively. No statistically significant increases in the mean number of micronucleated PCEs per 1000 PCEs over these control values were seen at any hexythiazox technical dose. The cyclophosphamide positive control induced the appropriate response with statistically significant ($p <= 0.05$) increases in the mean numbers of micronucleated PCEs per 1000 PCEs of 27.7 ± 4.56 and 28.4 ± 3.80 in males and females, respectively. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow of test article-treated mice after any dose or treatment time.

3. Structure-Activity Relationship (SAR)

No closely related structural analogs were identified.

4. Mode of Action Studies

No mode of action data were submitted.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee considered the following for a weight-of-evidence determination on the carcinogenic potential of ~~metam sodium~~ *[hexythiazox]:*

1. Carcinogenicity

Mouse

- Administration of hexythiazox resulted in the induction of liver tumors in female B6C3F1 mice. There were significant increasing trends for liver adenomas ($p<0.01$), carcinomas ($p<0.05$) and combined adenomas/carcinomas ($p<0.01$). There were also significant differences in the pair-wise comparison of the high dose with the control for adenomas ($p<0.01$), carcinomas ($p<0.05$), and combined adenomas and carcinomas ($p<0.01$). There was no evidence of carcinogenicity in male mice at any dose level. **The CARC considered the liver tumors, seen at the high dose, in female mice to be treatment-related.**

- *Adequacy of Dosing*: Dosing at the high dose in the mouse study was considered to be adequate in both sexes for assessing the carcinogenic potential of hexythiazox. This was based on decreased body weight gains, increased absolute/relative liver weights in males and/or females, and the presence of non-neoplasic liver nodules.

Rat

- Administration of hexythiazox resulted in the induction of tumors of the mammary gland in male Fischer 344 rats. There was a significant increasing trend at $p<0.01$ and a significant difference in the pair-wise comparison of the high dose with the control for fibroadenomas at $p<0.05$. There was no evidence of carcinogenicity in female rats at any dose level. **The CARC considered the mammary gland tumors in male rats to be treatment-related.**

- *Adequacy of Dosing:* Dosing at the high dose was considered to adequate in both sexes for assessing the carcinogenic potential of hexythiazox based on the decreases in body weight and increases in testicular and ovarian weights.

Mutagenicity

There is no mutagenic concern for hexythiazox.

Structure Activity Relationship

No closely related structural analogs were identified.

Mode of Action

No mode of action data were submitted for this chemical.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified hexythiazox as **"Likely to be Carcinogenic to Humans"**. This classification was based on tumors in 2 species: a treatment-related increase in benign and malignant liver tumors in female mice and the presence of mammary gland tumors (fibroadenomas) in male rats, with incidences exceeding that of the laboratory's historical controls. Although the rat mammary gland tumors were benign, they are uncommon in male rats (the laboratory's incidence rate was only 0-2%). There is no mutagenic concern for hexythiazox.

[Note: While the majority voted for the "Likely" classification, the remaining vote supported a "Suggestive Evidence of Carcinogenic Potential". This was based on a treatment-related increase in tumors at the high dose only in both rats and mice, and no mutagenicity concerns.]

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The CARC concluded that the evidence as a whole was not strong enough to warrant the use of a linear low dose extrapolation model applied to the animal data (Q_1*) for a quantitative estimation of human risk, based on the common liver tumors (benign and malignant) only observed in high dose female mice, and benign mammary gland tumors, only observed in high dose male rats. Also, there is no mutagenic concern for hexythiazox.

The NOAEL of 2.5 mg/kg/day, from the one year toxicity feeding study in the dog, used for establishing the chronic Reference Dose (RfD) is approximately 65-fold lower than the lowest dose (163 mg/kg/day) that induced tumors. Thus, the chronic RfD of 0.025 mg/kg/day would be protective of all chronic effects including potential carcinogenicity of hexythiazox.

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